Departement für Kleintiere, Klinik für Kleintiermedizin
der Vetsuisse-Fakultät Universität Zürich

Direktorin: Prof. Dr. Claudia Reusch

Continuous Glucose Monitoring System: a new tool to assess blood glucose concentrations in cats with diabetes mellitus

Inaugural-Dissertation

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

Simona Gianna Dietiker-Moretti

Tierärztin
von Castel San Pietro, Schweiz

genehmigt auf Antrag von

PD Dr. Eric Zini, Referent

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Summary

Diabetes mellitus is one of the most common endocrine diseases of cats. Administration of insulin and feeding low-carbohydrate high-protein diets represent the mainstay of treatment. After diagnosis, regular examinations are necessary to monitor glycemia and adjust insulin therapy.

Portable blood glucose meters (PBGM) were developed to improve glycemic control in diabetic humans and were validated for use in animals. In the last decade continuous glucose monitoring systems (CGMS) that measure glucose concentrations in the interstitial fluid of the subcutaneous tissue have been developed for humans. A new generation of CGMS allows frequent measurements of interstitial glucose concentrations and instantaneously displays the recorded data on a portable monitor.

The aim of our studies was to evaluate the new generation CGMS Guardian REAL-Time® for use in diabetic cats. Accuracy and precision were calculated *in vivo* and *in vitro*. The CGMS was clinically reliable and suitable for real-time measurement in cats. Further, performance of the CGMS to generate glucose curves and deciding about treatment was compared to that of a PBGM. Insulin dose recommendations did not differ between glucose curves assessed with CGMS and PBGM. Of note, glucose nadirs were lower with the CGMS, suggesting that the new device detects hypoglycemic periods that may not be identified with the PBGM. Using CGMS is expected to improve glycemic control and ameliorate quality of life in diabetic cats.

Zusammenfassung

Diabetes mellitus ist eine der häufigsten Endokrinopathien der Katze. Insulin und eine kohlenhydratarme Diät bilden die Kernpunkte der Therapie. Nach Diagnosestellung sind regelmässige Nachkontrollen des Blutzuckerspiegels wichtig, um die Therapie der Stoffwechselsituation der Patienten anzupassen.
Portable Glukosemessgeräte (PBGM) wurden in der Humanmedizin entwickelt und für Tiere validiert. Mittlerweile werden beim Mensch auch sog. CGMS verwendet, die die Glukosekonzentration der interstitiellen Flüssigkeit kontinuierlich messen und diese auf einem Monitor übertragen.
Ziel unserer Studien war, das neue CGMS Guardian REAL-Time® bei diabetischen Katzen zu evaluieren. Präzision und Richtigkeit wurden *in vivo* und *in vitro* ermittelt. Das CGMS zeichnete sich als zuverlässig und geeignet für die Echtzeitmessung der Glykämie aus. Zusätzlich wurde seine Verlässlichkeit für die Erstellung von Glukosekurven während Nachkontrollen und für entsprechende Therapieentscheidungen im Vergleich zu einem PBGM evaluiert.
Die Dosisempfehlungen basierend auf CGMS Kurven waren ähnlich wie beim PBGM. Die häufigere Erfassung niedriger Glukosewerte beim CGMS deutet auf eine bessere Erkennung von hypoglykämischen Perioden als bei der Verwendung des PBGM hin.
Die Anwendung von CGMS wird aus unserer Sicht zu einer Verbesserung der Messung der Glukosewerte und dadurch zu einer Steigerung der Lebensqualität diabetischer Katzen beitragen.

Artikel

„Evaluation of a novel real-time continuous glucose-monitoring system for use in cats“, publiziert im Journal of Veterinary Internal Medicine, 2010.

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1 Introduction

Measurement of blood glucose concentrations and the generation of blood glucose curves are integral parts of monitoring diabetes in cats.[1,2] Multiple blood samples during a defined period of time are required to obtain glucose curves that allow adjustment of medication. In general, samples are collected every 1–2 hours over 10–12 hours by venipuncture or capillary blood sampling in cats. Repeated handling or restraining the cats can artifactually elevate blood glucose concentrations because cats are particularly sensitive to stress-induced hyperglycemia. Consequently, the interpretation of the glucose curve may be difficult because of the potential confounding influence of stress. Another limitation is that even with numerous blood samplings the glucose nadir or peak may be missed because of the 1–2-hour intervals between measurements.[3,4]

To assess glucose concentrations more frequently, continuous glucose-monitoring systems (CGMS) have been developed for diabetic humans almost 2 decades ago; their use has recently also been described in other species, including the cat.[5–7] The systems measure glucose concentrations in the subcutaneous interstitial fluid, which have been shown to correlate well with that obtained in whole blood.[8,9] In humans, the average delay between a change of the glucose concentration in blood versus interstitial fluid was approximately 5 minutes, thus making the CGMS reliable for real-time monitoring. Because of the high performance, the CGMS is increasingly considered an essential device to improve treatment of human diabetes mellitus.[8,10,11]

A CGMS was used in 16 diabetic cats and there was a good correlation between glucose concentrations measured in the interstitial fluid and in the capillary or peripheral blood.[5] In addition, the system unveiled an excessively low glucose nadir in insulin treated diabetic cats, thus allowing treatment to be modified. In 2 other studies, CGMS were used successfully to obtain glucose curves in diabetic cats.[6,7] A drawback of all CGMS previously used in cats is that the monitoring device had to be fixed to the animal, and that the recorded data had to be downloaded manually on a computer in order to be analyzed.[5–7]

The Guardian REAL-Time CGMS belongs to a new generation of CGMS designed for

diabetes monitoring. It provides interstitial glucose concentrations in real-time and enables on-screen recording of data over a 24-hour period. This allows diabetic humans to self-assess their glucose concentrations and to recognize potential episodes of hypoglycemia as early as possible. Further, the monitor can be kept separate from the body. These innovations are also expected to simplify the use of the instrument in cats and, in particular, to substantially decrease the stress for the generation of glucose curves. Recently, the novel CGMS was used in 1 diabetic cat and the device was well tolerated and promptly identified an episode of hypoglycemia caused by an insulin overdose.[12]

The purpose of the present study reported was to further investigate the performance of the Guardian REAL-Time CGMS for use in cats. The clinical and analytical accuracy were studied, with special attention paid to potential sources of error.

2 Materials and Methods

2.1 Cats

The study was performed with 39 cats, including 34 client-owned diseased cats, and 5 healthy experimental cats[a] (Veterinary Office of Zürich, Switzerland, permission nr. 94/2008). Among the client-owned cats, 32 were diagnosed with diabetes mellitus, 5 of which had diabetic ketoacidosis. Two of the client-owned cats had suspected insulinoma based on severe hypoglycemia that poorly responded to treatment and based on a pancreatic mass that was identified by abdominal ultrasonography. The median age of the 34 cats was 12 years (range: 2–17 years). Twenty-three (67.6%) were neutered males and 11 (32.4%) were spayed females. Twenty-eight cats (82.4%) were domestic short- or longhair, 2 were Norwegian forest cats, and 1 each was a Birman, Persian, Ragdoll, or Egyptian Mau cat. The median age of the 5 experimental cats was 8 months (range: 6–11 months), and all were intact male domestic shorthair. Young cats were used because they were available from another experiment. They were clinically healthy based on physical examination and blood work (data not shown).

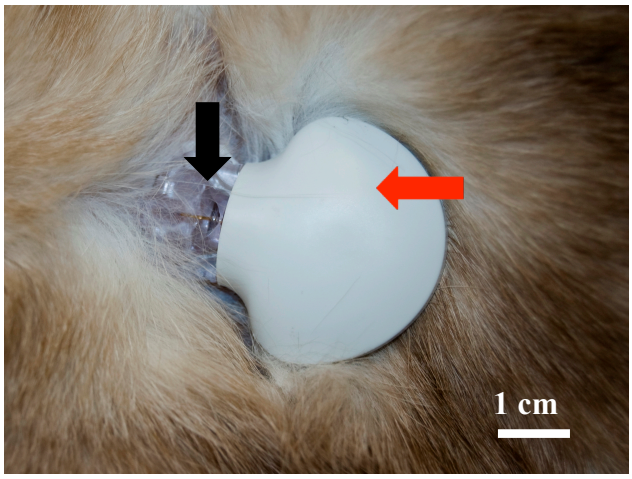
2.2 CGMS

The Guardian REAL-Time[b] system for continuous glucose monitoring consists of a disposable sensor, a transmitter and a pager-sized monitor (Fig 1). The sensor is housed in flexible 1.5 cm tubing with a membrane-covered side window that allows the active electrode to interact with the interstitial fluid. The sensor is placed in the subcutaneous tissue by means of a 22 G needle. Glucose in the interstitial fluid undergoes an electrochemical reaction on the glucose oxidase-containing electrode that generates a small electric current. This will be subsequently converted to glucose concentration (mg/dL). The sensor is connected to a transmitter that transmits data over a maximal distance of 3 m to a pager-sized monitor; the monitor displays data in real-time for up to 24 hours. Data are collected every 10 seconds and a mean value computed every 5 minutes. The sensor can be used for up to 72 hours. The monitor has the capability to record interstitial glucose concentrations for up to 1 month before downloading on a computer for further analysis. Notably, the monitor shows glucose concentrations between 40 and 400 mg/dL; concentrations beyond this range are correctly recorded by the CGMS but need to be downloaded to be analyzed.

Figure 1.

Use of the Guardian REAL-Time continuous glucose-monitoring system in cats. (A) The sensor (black arrow) measures interstitial fluid glucose in the subcutaneous tissue of the thorax and is connected to the transmitter (red arrow). (B) Recorded glucose concentrations are transmitted wirelessly to the monitor and displayed on the screen in real time.

A



B

After placement of the sensor, the CGMS requires a 2-h initialization period. During this interval interstitial glucose concentrations are not provided. Calibration needs to be performed by measuring blood glucose concentrations with a rapid method such as a portable blood glucose meter. The recorded value is immediately transcribed in the monitor of the CGMS to initiate readings; if blood glucose is <40 or >400 mg/dL calibration needs to be postponed until the concentration reaches 40–400 mg/dL. The system is recalibrated after 6 hours and subsequently at least twice daily.

In the present study, the CGMS sensor was placed in the subcutaneous tissue of the thorax of cats, at the 6th or 7th intercostal space, and about halfway between the spine and sternum. In brief, a 3x3 cm skin area was clipped and disinfected. The sensor was injected subcutaneously and was fixed to skin with tape and protected with a soft bandage placed around the chest. For calibration, the capillary blood glucose concentration was measured from the inner pinna with a portable blood glucose meter (PBGM).[13] Glucose concentrations were recorded with cats hospitalized in cages; the monitor was fixed to the cage door. The distance between transmitter and monitor was <1.5 m. All procedures were performed in awake cats.

The readings of the CGMS were compared with those of the PBGM AlphaTRAK[c] used as a reference. The AlphaTRAK was shown to be precise and accurate[13]; the glucose

concentrations measured in the capillary blood did not differ from those measured in whole blood with the reference laboratory hexokinase method.[13]

2.3 Adverse reactions using the CGMS

During monitoring of glucose concentrations, attention was paid to possible abnormal behavior because of the bandage that was used to keep the sensor in place. We recorded whether the cat tried to remove the sensor, developed aggressiveness, or showed decreased appetite. When the bandage and sensor were removed, 1 of the investigators (Simona Moretti or Dr. Flurin Tschuor) recorded adverse skin reactions, especially at the site of sensor placement.

2.4 Accuracy of the CGMS

To compare glucose concentrations measured with CGMS to the PBGM, paired samples were taken in the hypoglycemic range (<90 mg/dL), in the euglycemic range (90–180 mg/dL), and in the hyperglycemic range (>180 mg/dL). From each cat, 10–15 paired glucose measurements were collected during the 1st 2–3 days of glucose monitoring. At the same time glucose concentrations were measured with the PBGM, and values shown by the monitor of the CGMS were noted. For interstitial glucose concentrations <40 or >400 mg/dL (ie, not shown by the monitor) the exact sampling time was noted and the values were later downloaded from the CGMS.

2.5 Variability of paired CGMS readings in vivo

Two CGMS devices were simultaneously used for 24 hours in 5 diabetic cats. The CGMS sensors were placed symmetrically on the left and right side of the thorax. The 2 CGMS were calibrated every 10–12 hours with the same glucose measurement obtained with the PBGM.

2.6 Variability of paired CGMS readings in vitro

To verify whether technical characteristics of the CGMS contributed to variability of paired readings, *in vitro* tests were performed using solutions mimicking the hypoglycemic, euglycemic, and hyperglycemic range. Glucose[d] was added to saline to yield solutions with glucose concentrations of approximately 50, 90, and 300 mg/dL. Two CGMS devices were simultaneously used for 12 hours in each solution. The solutions were put in a closed box to protect them from light exposure; they were kept at room temperature.

2.7 Time delay of the CGMS

To investigate the time delay between a rapid change in blood glucose concentrations and the rise in interstitial fluid glucose recorded by CGMS, an IV bolus of glucose was administered to 5 healthy cats. The CGMS was placed 6 hours before IV administration of glucose. Glucose concentrations were recorded in the interstitial fluid with the CGMS, starting just before the bolus was given and for 2 hours thereafter. During the same period, glucose concentrations were also measured in the capillary blood with the PBGM (before and 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the bolus).
The test was performed in fasted cats sedated with tiletamine/ zolazepame and anesthetized with propofol.[f] Cats were acclimated to anesthesia for 1 hour. Thereafter the glucosed bolus of 1 g/kg was administered via the femoral vein. The time difference between the points of maximal rise of glucose concentration measured in the blood and in the interstitial fluid was calculated; this calculation had been used to quantify the delay to observe a change in interstitial glucose in humans.[14]

2.8 Statistical Analysis

Accuracy between results of the CGMS and the PBGM was evaluated with statistical methods and using a clinically oriented approach. Using the method of residuals, the differences between results of the CGMS and the reference method were plotted.[15] The clinical accuracy of CGMS readings was examined by use of the Clarke error grid analysis, as described in cats.[16,17] The grid system assigns CGMS measured values (y-axis) versus actual blood glucose

values (reference PBGM, x-axis) to 5 zones (A through E) and is based on the assumption that the clinical goal is to maintain blood glucose concentrations between 70 and 180 mg/dL. Measurements in zones A and B are clinically accurate in that they lead to clinically correct treatment decisions. The CGMS readings in zone A deviate from the reference value by no >20%. The CGMS readings in zone B represent benign errors and deviate from reference values by >20%; however, they would either not lead to a change in treatment, or treatment would not have any harmful effects. Values in zones C, D, and E would lead to relevant treatment errors or failure to initiate treatment. Values in zone C would lead to unnecessary correction or overcorrection of the acceptable glucose concentration and would cause the actual blood glucose concentration to fall below 70 mg/dL or to increase above 180 mg/dL. Zone D represents potentially dangerous errors of failing to detect and to treat actual blood glucose values that are outside the target range, because CGMS readings are within the target range. The CGMS readings in zone E are opposite to the actual blood glucose values, and therapeutic actions would be opposite to those indicated.

Because readings obtained with the CGMS may occasionally fluctuate for 5–15 minutes in cats, the accuracy was also calculated by including only measurement that were preceded by stable interstitial glucose concentrations over 30 minutes. Glucose readings were considered stable if their calculated coefficient of variation was below 10%.

To assess reading variability of 2 CGMS devices used simultaneously in the same cat, the Pearson correlation coefficient and the mean absolute difference between paired sensor glucose values were calculated. Concordance in the simultaneous measurements was determined by calculating the percentage of data that could both be classified in the normal, high, and low glucose range.[18] However, because paired readings can be similar but could fall into 2 different glycemic ranges, thus providing discordant results but with negligible clinical relevance, we included an additional criteria to calculate concordance; paired samples had to show a difference of at least 10% to be classified as discordant. The same tests were used to assess variability *in vitro*.

To quantify the time interval between an increase of glucose concentrations in peripheral blood and interstitial fluid, the time difference was calculated for the maximal increase in the slope of the 2 glucose curves computed with 2nd derivatives.[14]

Significance was set at $P < .05$. Data were analyzed with a commercially available software.[g]

3 Results

3.1 Practical use of the CGMS

The placement of the sensor and transmitter, and the visualization of the data in real-time on the monitor, were successful and easy to perform in each cat. No adverse skin reactions were observed at the site of sensor placement and none of the cats tried to remove the sensor or showed abnormal behavior in relation to the bandage.

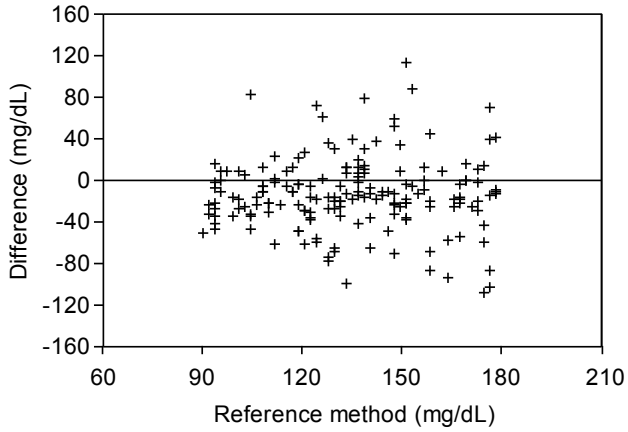
3.2 Accuracy of the CGMS

Four hundred and fourty-eight paired samples were taken with the CGMS and the PBGM. Based on the latter, 67 samples were in the hypoglycemic range, 176 in the euglycemic range, and 205 in the hyperglycemic range. The Bland and Altmann difference plots are shown in Figure 2; the mean ± 2 standard deviations (2 SD) difference from reference was -12.7 ± 70.5 mg/dL in the euglycemic range, -12.1 ± 141.5mg/dL in the hyperglycemic range, and -1.9 ± 40.9 mg/dL in the hypoglycemic range. The percentage of underestimated glucose readings was higher than that of overestimated values at normal (69.9 versus 27.3%), high (54.6 versus 42.9%), and low (56.7 versus 32.8%) blood glucose concentrations; values identical to reference were recorded in 2.8, 2.5, and 10.5% of measurements, respectively. Interstitial glucose concentrations differed by >100 mg/dL from the reference PBGM in 1.7% of cases in the euglycemic range, in 10.2% of cases in the hyperglycemic range and in no case in the hypoglycemic range. In the same ranges, interstitial glucose differed by >50 mg/dL in 17.0, 34.1, and in 1.5% of cases, respectively. In the hypoglycemic range, a deviation from the reference PBGM between 25 and 50 mg/dL was recorded in 22.4% of cases.

Figure 2.

Scatterplots of the differences between blood glucose concentrations obtained by use of the Guardian REAL-Time continuous glucose-monitoring system versus concentration obtained with the reference portable blood glucose meter AlphaTRAK at (A) normal, (B) high, and (C) low glucose concentrations in cats.

A



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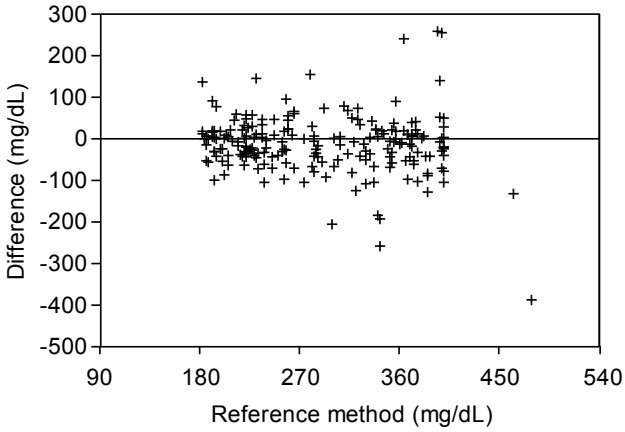

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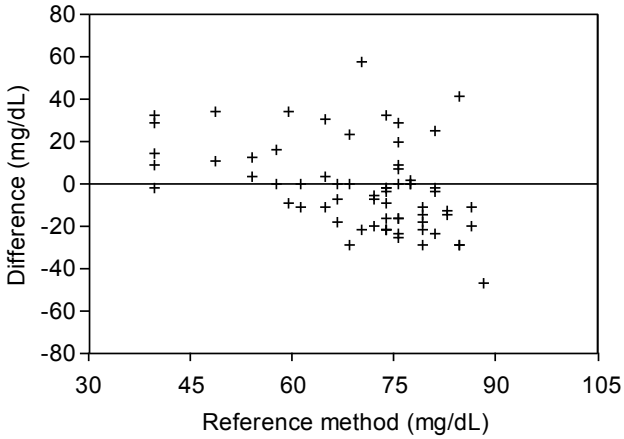


Results of the Clarke error grid analysis are reported in Figure 3. In the euglycemic range, the CGMS provided measurements that were in the clinically acceptable zones A and B in 63.1 and 36.9%, respectively, of cases. No reading was in zone C, D, or E. In the hyperglycemic range 74.6% of measurements were in zone A, 21.5% in zone B, and 3.9% in zone D. Measurements in zones C or E were not recorded. In the hypoglycemic range 64.2% of measurements were in zone A, 26.9% in zone B, and 9.0% in zone D. Readings in zones C or E were not recorded.

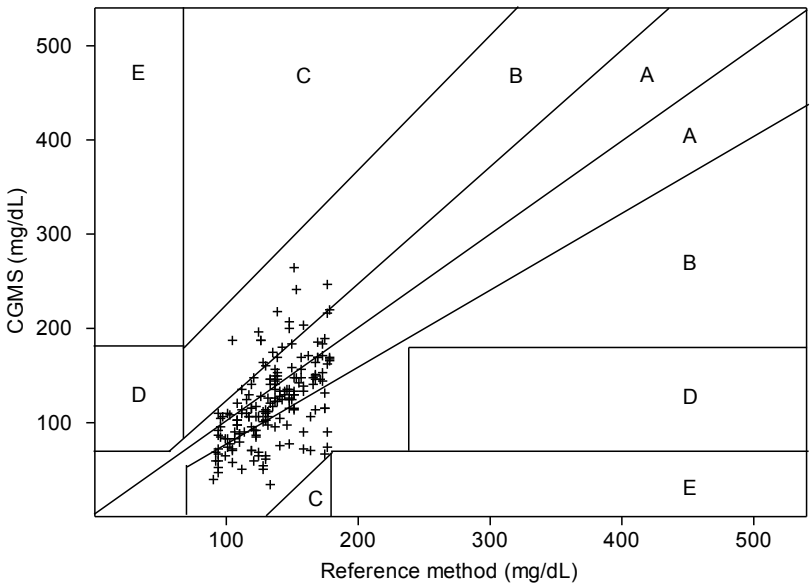
Similar results were obtained by including only CGMS readings that were preceded by a 30-minute period of stable interstitial glucose concentrations (388 paired samples). In the euglycemic range, mean ± 2 SD difference from reference was -6.7 ± 71.9, -1.9 ± 131.3

mg/dL in the hyperglycemic range, and -2.3 ± 38.8 mg/dL in the hypoglycemic range. Based on error grid analysis, the CGMS provided measurements in the euglycemic range that were in zones A and B in 64.7 and 35.3% of cases, respectively. No reading was in zones C to E. In the hyperglycemic range, 76.4% of measurements were in zone A, 21.6% in zone B, and 2.0% in zone D. Measurements in zones C or E were not recorded. In the hypoglycemic range 63.5% of measurements were in zone A, 26.9% in zone B, and 9.6% in zone D. Readings in zones C or E were not recorded.

Figure 3.

Error grid analysis for the Guardian REAL-Time continuous glucose-monitoring system (CGMS) in cats. Results of the CGMS that fall in zone A deviate from the reference method value by no >20%, or the CGMS value and the referece method value are <70 mg/dL. Results of the CGMS that fall in zone B deviate from the reference method value by >20%, but the treatment decision relying on the results of the CGMS would not cause unacceptable treatment errors. (A) At normal glucose concentrations the CGMS yielded measurements only in zones A or B. (B) At high glucose concentrations the CGMS yielded 96.1% of measurements in zones A or B and 3.9% in zone D (relying on CGMS value would result in a failure to detect glucose concentrations outside the reference range). (C) At low glucose concentrations the CGMS yielded 91.0% of measurements in zones A or B and 9.0% in zone D. None of the measurements was in zone C (relying on CGMS value would result in unnecessary corrections in insulin dosage) or E (relying on the CGMS value would result in erroneous treatment with insulin).

A



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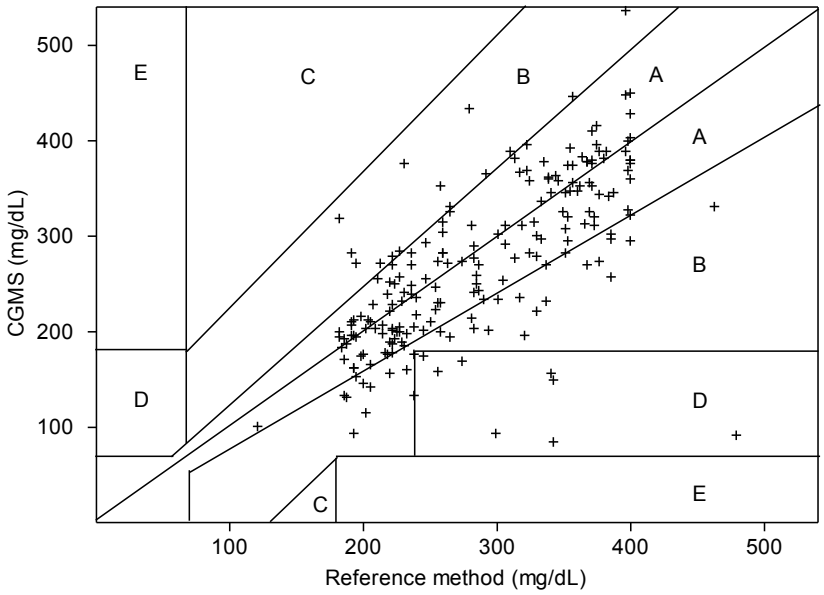

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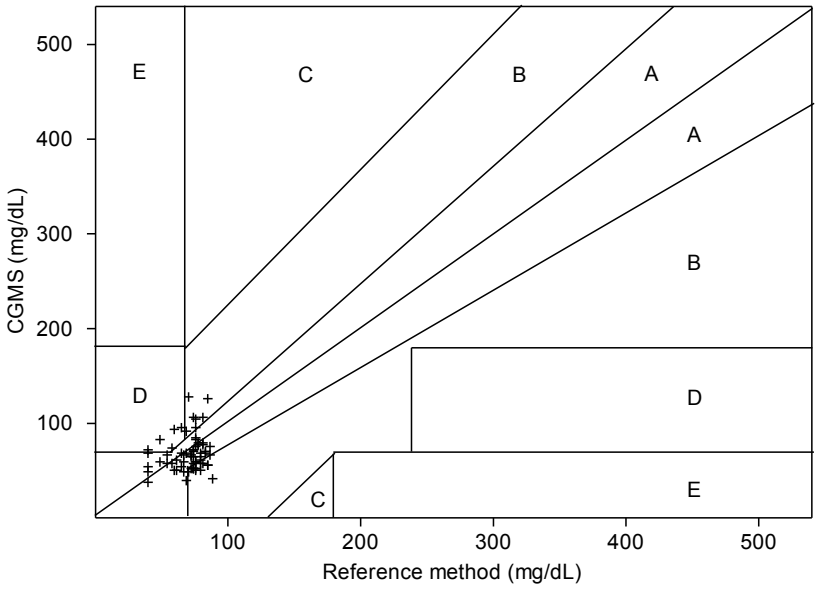


3.3 Variability of paired CGMS readings

The 1,445 paired sensor values correlated significantly ($r = 0.95$, $P < .0001$, Fig. 4). The correlation coefficient was lower for readings in the hypoglycemic range ($r = 0.37$) than in the euglycemic ($r = 0.64$) or hyperglycemic ($r = 0.76$) range (Table 1).

The mean ± 2 SD difference in interstitial glucose concentrations of all paired measurements was 14.3 ± 90.0 mg/dL; the absolute difference between paired readings was lower in the low (6.1 ± 25.6 mg/dL) than in the normal (9.0 ± 42.5 mg/dL) or high (41.9 ± 102.4 mg/dL) glycemic range. When the interstitial glucose values measured with 1 CGMS were classified as being in the euglycemic, hyperglycemic, or hypoglycemic range, 95.7% of all pairs were concordant (Table 2). Of the remaining nonconcordant pairs, 1 interstitial glucose value was classified as in the euglycemic range and the corresponding in the hyperglycemic range (2.8%), or 1 interstitial glucose value was classified as in the euglycemic range and the other in the hypoglycemic range (1.5%). Pairs with 1 value in the hyperglycemic range and the other in the hypoglycemic range were not observed. When analyzed separately for the respective glycemic ranges, readings were 93.9, 96.1, and 100% concordant at normal, high, and low glucose concentrations, respectively.

In vitro, paired sensor values correlated significantly (r = 0.99, P < .0001); the correlation coefficient was slightly lower for paired readings in the low glucose range (r = 0.63) than in the euglycemic (r = 0.73) or the hyperglycemic (r = 0.99) range. The mean ± 2 SD difference of paired readings was 11.6 ± 14.9 mg/dL at normal, 8.0 ± 8.4 mg/dL at high and 9.0 ± 16.6 mg/dL at low glucose concentrations. Concordance was 100% in each case.

Table 1.

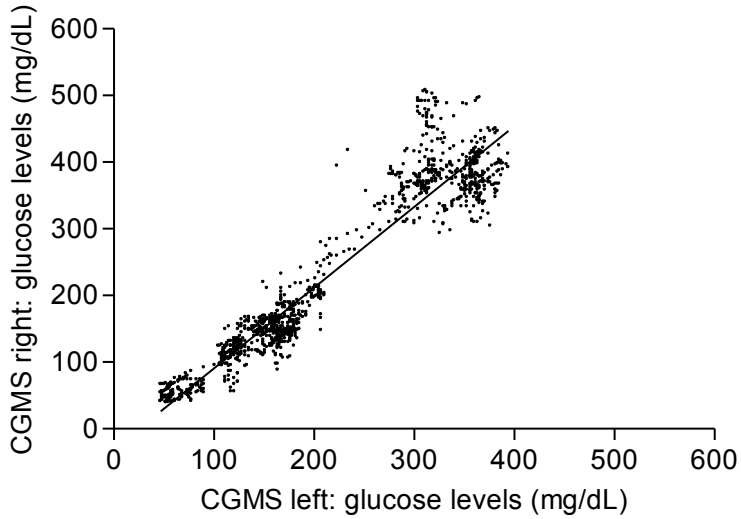
Correlation coefficients, 95% confidence interval (CI), and significance level of glucose concentrations measured simultaneously by 2 continuous glucose-monitoring systems on the left and right side of the thorax; values were subdivided according to glycemic range.

Glycemia Range	Pearson's Correlation Coefficient (*r*)	CI 95%	Significance
Euglycemia	0.64	0.59–0.69	P < .0001
Hyperglycemia	0.76	0.73–0.80	P < .0001
Hypoglycemia	0.37	0.23–0.50	P < .0001
Total	0.95	0.95–0.96	P < .0001

Figure 4.

(A) Correlation of continuous glucose-monitoring system (CGMS) glucose values measured on the left and right side of the thorax simultaneously. (B) Glucose curves of 2 simultaneously used CGMS (left and right side of the thorax); paired readings are very similar during the entire period of analysis.

A



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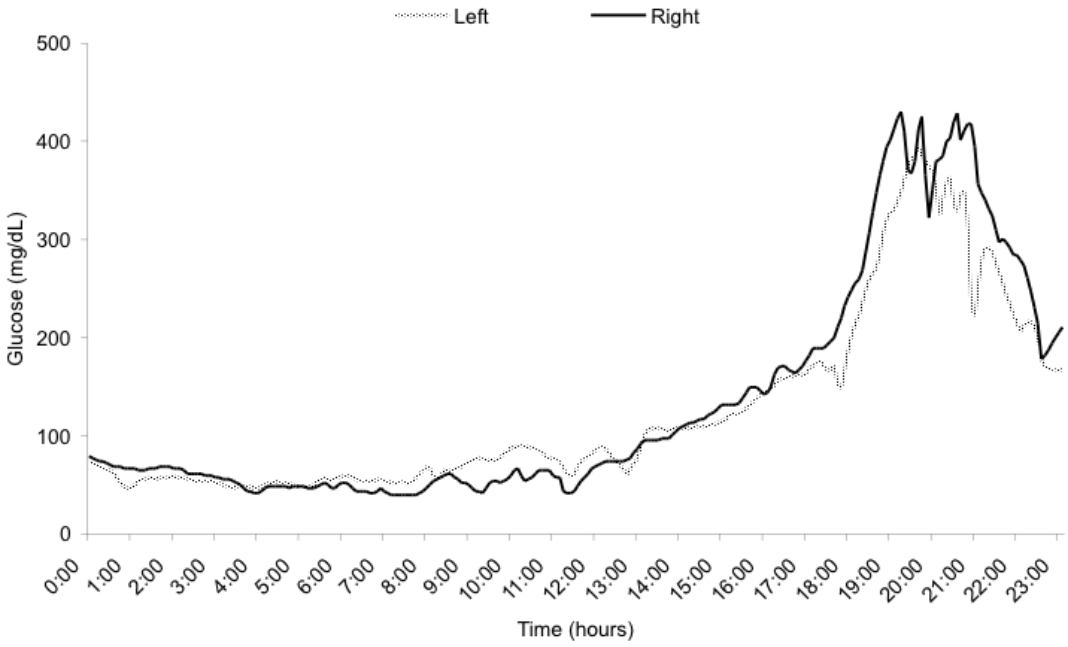

Table 2.

Concordance of glucose values simultaneously measured with the continuous glucose-monitoring system on the left and right side of the thorax according to glycemic range.

		Nonconcordant Values (%)		
Glycemic Range	Concordant (%)	Euglycemic/ Hyperglycemic	Euglycemic/ Hypoglycemic	Hyperglycemic/ Hypoglycemic
Euglycemia	93.9	2.6	3.5	
Hyperglycemia	96.1	3.9		0
Hypoglycemia	100		0	0
Total	95.7	2.8	1.5	0

3.4 Time delay of the CGMS

In the capillary blood of healthy cats, the maximal glucose concentration was always recorded immediately after the IV injection of glucose bolus; the glucose concentration progressively decreased thereafter. In the interstitial fluid, the measured glucose concentrations gradually increased and reached the maximal concentration after 35.0 minutes; after that, the interstitial glucose concentration gradually decreased. The delay from the time of the IV injection of glucose bolus to the maximal rising slope of the glucose curve in the interstitial fluid was 11.4 minutes (range: 8.8–19.7 minutes).

4 Discussion

The Guardian REAL-Time CGMS was successfully used in cats. No adverse skin reactions were observed at the site of sensor placement and all cats tolerated the bandage. The latter was likely because of the fact that the monitor of the new CGMS can be kept separate from the cat, thus substantially reducing discomfort. Different from the previous generation of CGMS,[5–7] the new device allows to visualize the interstitial glucose concentrations in real-time and to scroll the recorded values over the last 24 hours. Real-time monitoring performed with the new CGMS may thus be particularly useful with uncooperative cats or whenever the measurement of the blood glucose concentration with PBGMs is impractical. A drawback of the Guardian REAL-Time system is that the system only calibrates if the blood glucose concentrations are between 40 and 400 mg/dL; otherwise the monitoring cannot be started. For this reason, the calibration had to be postponed by 1–3 hours in 6 diabetic cats in the present study to allow insulin therapy to decrease blood glucose below 400 mg/dL.

The results of the error grid analysis showed that the clinical accuracy of the CGMS was satisfactory in the euglycemic and hyperglycemic range, and only slightly less in the hypoglycemic range. No reading was assigned to zone C (ie, leading to correction of acceptable blood glucose concentration) or E (ie, leading to opposite therapeutic actions to those indicated) at any blood glucose concentration. However, 9.0 and 3.9% of readings in the hypoglycemic and hyperglycemic ranges, respectively, were in zone D. Values in zone D can lead to potential dangerous errors by failing to detect or to treat blood glucose concentrations that are outside the reference range. By including only CGMS readings preceded by a 30-minute period of stable interstitial glucose concentrations, the results of the error grid analysis were comparable; this suggests that the clinical accuracy of the CGMS is not affected by short-lasting fluctuations of the interstitial glucose concentration.

To better assess interstitial glucose curves with rapid glucose fluctuations, the recently introduced continuous glucose-error grid analysis has been proposed.[19] This method takes into consideration the effect of glucose trends of the interstitial glucose curve, in addition to single readings; it has been developed to improve estimation of clinical accuracy of CGMS in humans. In the present study, we opted not to use the continuous glucose-error grid analysis to avoid excessive stress or risk of anemia, because peripheral or capillary blood samples need to be collected every 15 minutes.

Although the mean differences of interstitial glucose concentrations measured with the CGMS versus reference values were minimal at any blood glucose concentration, the spread

of results as shown with Bland and Altmann plots was wide, in particular in the hyperglycemic range; based on 2 SD the difference was up to ± 141.5mg/dL. However, despite this large variation, clinical accuracy assessed with the error grid analysis remained good because 95.6% of readings were in zone A or B. In contrast, in the hypoglycemic range, the difference between the 2 methods based on 2 SD was up to ± 40.9 mg/dL, and a deviation from reference between 25 and 50 mg/dL was observed in 22.4% of readings. When blood glucose concentrations are low, differences of this magnitude may be important and lead to treatment errors, as indicated by the relatively high percentage of readings falling in zone D (9.0%) in the error grid analysis. Therefore, if CGMS measurements are at the lower end of the normal glucose range or below, it is advisable to periodically assess blood glucose concentrations with another method. In the euglycemic range, difference from reference based on 2 SD was ± 71.9 mg/dL; however, despite the large variation, all readings would have led to clinically correct treatment decisions according to error grid analysis.

The overall variability of simultaneous interstitial glucose readings obtained with 2 CGMS was good, with both a high correlation coefficient ($r = 0.95$; $P < .0001$) and a high percentage of concordance (95.7%). Of note, the correlation coefficient in the hypoglycemic range was low ($r = 0.37$), which may suggest inferior performance of the device at low glucose concentrations. However, the mean and absolute differences between paired readings were relatively small (6.1 ± 25.6 mg/dL) and the concordance was 100%. Thus, we consider the low correlation coefficient of paired readings in the hypoglycemic range of little clinical relevance. In the euglycemic and hyperglycemic range, the variability of paired CGMS readings was very good. The large difference observed at high blood glucose concentrations, as assessed with 2 SD (± 102.4 mg/dL), does not seem to have a major influence on treatment decision because only 3.9% of measurements were recorded as hyperglycemic while actually being in the normal range. Accordingly, readings obtained with different CGMS can be considered comparable at all blood glucose concentrations, similar to what has been described in humans.[18] Results achieved *in vitro* were better than *in vivo* for both correlation analysis and mean differences. At decreasing glucose concentrations the correlation coefficient was slightly lower than at normal or high glucose concentrations, confirming the slight inferior performance of the device with lowering glucose concentration.

Based on the IV administration of a glucose bolus in healthy cats, the CGMS recorded a maximal rise in interstitial glucose with a median delay of 11.4 minutes, which is close to the delay of 10 minutes previously observed in dogs.[20] This suggests that changes in blood glucose concentrations are rapidly detected in the interstitial fluid, thus making the device

reliable for real-time monitoring under clinical conditions. Of note, we used healthy young cats in our study. In diabetic cats, which typically are older and often slightly dehydrated, an equilibrium of the glucose concentration between blood and interstitial fluid may possibly be reached slightly later. However, to test this hypothesis glucose would need to be injected in diabetic cats, leading to an increase of plasma osmolarity to a dangerous level. In addition, it is important to note that the glucose bolus was administered under anesthesia. Peripheral capillary pressure may have been decreased, thus reducing the glucose shift from the vascular to the interstitial compartment.

In summary, the novel CGMS provides clinically accurate and reproducible measurements in the euglycemic and hyperglycemic range; the clinical accuracy was slightly less in the hypoglycemic range. In the latter case, or when interstitial glucose readings are at the lower end of the normal range, it may be advisable to assess blood glucose concentration with a reference method to confirm the CGMS results. The short interval between an increase of glycemia and a rise in interstitial glucose makes the CGMS useful for real-time monitoring in cats.

5 References and Footnotes

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Footnotes

a Outstation Stigenhof, Oberembrach, Switzerland
b Guardian REAL-Time continuous glucose monitoring system, Medtronic, Münchenbuchsee, Switzerland
c AlphaTRAK portable blood glucose meter, Abbott Animal Health, Maidenhead, UK
d Glukose 50%, Kantonsapotheke, Zürich, Switzerland
e Zoletil 100, Virbac, Glattbrugg, Switzerland
f Propofol 2%, Fresenius Kabi, Stans, Switzerland
g GraphPad Prism 4.0, GraphPad, San Diego, CA

Artikel

„Comparison of a continuous glucose monitoring system with a portable blood glucose meter to determine insulin dose in cats with diabetes mellitus“,
publiziert im Journal of Veterinary Internal Medicine, 2011.

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1 Introduction

Diabetes mellitus is one of the most common endocrine diseases of cats and its incidence is increasing because of an increase in predisposing factors such as obesity and physical inactivity.[1–3] The mainstay of treatment of feline diabetes is insulin, generally combined with a high-protein, low-carbohydrate diet.[4] Assessing insulin requirement is a critical aspect of monitoring in diabetic cats because the dose may vary over time. For instance, an increase in the dose of insulin may be required in cats that develop concurrent disease, or discontinuation of insulin administration is advised when treatment results in clinical remission of diabetes mellitus. The history and results of a physical examination, serum fructosamine concentration, and blood glucose profiles are required for monitoring the response to insulin.

Blood glucose profiles can be generated in a hospital, or at home by cat owners, in which case they are evaluated later by a veterinarian.[5–7] Blood glucose profiles are usually made by measuring the blood glucose concentration every 1‑2 hours over an 8- to 10-hour period using a portable blood glucose meter (PBGM). To obtain better glycemic control, continuous glucose monitoring systems (CGMS) were developed for human diabetics and later evaluated for use in animals.[8–10] CGMS measure glucose in the subcutaneous interstitial fluid every few seconds, thus allowing the generation of more detailed glucose profiles.

Recently, a CGMS[a] of a new generation, which allows glucose readings every 5 minutes and instantaneous visualization of the recorded data on a separate screen, was successfully validated for use in cats. This instrument provided measurements in real-time and yielded clinically accurate and reproducible results.[11] In another report, the same CGMS allowed identification of an episode of hypoglycemia in a diabetic cat that had received an inappropriately high insulin dose.[12]

It is not reported whether treatment decisions based on glucose profiles obtained with a CGMS differ from those derived using a PBGM in cats. Therefore, the aim of the present study was to compare insulin doses recommended by internal medicine specialists based on the blinded assessment of paired glucose profiles generated with a new-generation CGMS and a reference PBGM in diabetic cats.

2 Materials and Methods

2.1 Diabetic cats

Fourteen client-owned diabetic cats were hospitalized to generate simultaneous paired 8–10 hour glucose profiles using a CGMS and a PBGM during a follow-up examination at the Clinic for Small Animal Internal Medicine, University of Zurich, Switzerland. The cats had been treated with insulin glargine[b] for a median of 4 weeks (range 0–26 weeks) before blood glucose profiles included in the study were generated. All cats were treated with insulin twice daily before the examination. Informed consent was obtained from the owners. The cats consisted of 9 neutered males, 1 intact male and 4 spayed females, and there were 10 European shorthair, 1 European-longhair, 1 Norwegian Forest, 1 Birman, and 1 Ragdoll cat. Median age was 12 years (range: 8–15 years). All the cats had been diagnosed with diabetes mellitus at our clinic, based on clinical signs, including polyuria, polydipsia, polyphagia and weight loss, and laboratory tests, including hyperglycemia, increased serum fructosamine concentration and glucosuria.

2.2 Continuous Glucose Monitoring System

The Guardian REAL-Time®,[a] CGMS consists of a disposable sensor, a transmitter, and a pager-sized monitor. The sensor is able to measure the glucose concentration in the interstitial fluid via an enzymatic reaction that generates a small electrical current. This signal is subsequently converted to a glucose concentration (mg/dL). The transmitter sends the data to the monitor where they are displayed in real-time. Measurements are made every 10 seconds and displayed on the monitor as 5-minute means. It should be noted that the monitor displays glucose concentrations from 40 to 400 mg/dL; concentrations outside this range are correctly recorded by the CGMS but need to be downloaded to be visualized.[11]

After starting the sensor, the CGMS needs a 2-hour period of initialization. Glucose values are not provided until the system is ready for calibration. For calibration, the cat's current glucose concentration is measured with a PBGM and entered into the device as a reference value. The CGMS needs to be further calibrated within 6 hours of initial calibration and then every 12 hours. Only values between 40 and 400 mg/dL can be used for calibration. If the blood glucose concentration is outside this range, calibration needs to be postponed until the

concentration has returned to within the range.
In accordance with a previous study,[11] the CGMS sensor was placed in the subcutaneous tissue of the lateral chest wall, at the 6th or 7th intercostal space, and about halfway between the vertebral column and sternum. A small area of skin in this region was clipped and disinfected with an alcohol solution.[c] After the skin was dry, the sensor was inserted under the skin through a disposable hypodermic needle and fixed to the patient with tape. The transmitter was connected to the sensor and a soft bandage was placed around the chest to protect the device.

2.3 Portable Blood Glucose Meter

The PBGM AlphaTRAK®,[d] specifically designed for dogs and cats, was used to obtain a 2nd glucose profile. This device was previously shown to provide precise and accurate measurements in cats[13] and is routinely employed in our clinic to measure capillary blood glucose concentrations in cats. The working range of the device is 20–500 mg/dL.

2.4 Generation of glucose profiles

All the cats received insulin glargine[b] and were fed at home before admission to the clinic, in the morning. A baseline capillary blood glucose concentration was determined using the PBGM and blood collected via ear puncture before examination and manipulation of the patient. After physical examination, venous blood samples were collected for hematological and biochemical analyses. Additional analyses were carried out when indicated.
The CGMS sensor was then placed and fixed to the animal as described above, and the monitor was secured to the cage door. Cats were housed individually in a cage from shortly after admission to late afternoon. They had free access to water but food was not provided. The CGMS was calibrated twice; once before the start of measurements and again 6 hours later. Glucose readings with the CGMS were first available 2 hours after 1st calibration. After the baseline measurement, glucose concentrations were measured every 2 hours with the PBGM. Immediately after the last glucose measurement with the PBGM, the CGMS was turned off.

2.5 Assessment of glucose profiles

Three clinicians with board certification in small animal internal medicine (Dr. Claudia Müller, Dr. Nadja Sieber-Rückstuhl, and Prof. Dr. Claudia CE Reusch) assessed the profiles generated using the 2 measuring devices and based on the results, recommended insulin dosages for the diabetic cats. Each clinician evaluated the glucose profiles independently, without knowledge of the insulin dose chosen by the others. The 21 paired profiles were split and randomly numbered, with different numbers for PBGM and CGMS profiles; with this method, examiners were blinded to which CGMS profile was paired with the respective PBGM profile. To evaluate PBGM profiles all measurements were made accessible, including the 1st glucose value obtained after admission at the clinic. To evaluate CGMS profiles there was a delay of 2 hours due to the initialization period. The following information was available for each profile for determining the insulin dose: amount of insulin administered before the blood glucose profile, whether the cat received 1 or 2 insulin injections per day, and body weight (≤4 kg, or >4 kg). Body weight was reported because in our clinic, diabetic cats >4 kg initially receive an additional 0.5–1 U of insulin per treatment. Other information, including history (eg, improvement of clinical signs), physical examination (in particular, whether body weight had increased or decreased), and serum fructosamine concentrations, were deliberately omitted to further minimize bias and ascertain that the recommended insulin dose was mainly based on the glucose profiles.

In our clinic, we define 3 concentration ranges for the glucose nadir; the ideal range is between 90 and 160 mg/dL. When the nadir is below 90 mg/dL (low range), the insulin dose is reduced by 0.5–1 U per injection. When the nadir is above 160 mg/dL (high range), the insulin dose is increased by 0.5–1 U per injection. The 3 investigators used this criterion during analysis of blood glucose profiles.

2.6 Statistical analysis

A commercial software[e] was used for statistical analysis. The glucose nadir, peak, and mean were recorded for each CGMS and corresponding PBGM profile, and the median and range of the differences among the nadirs, peaks, and means of the paired profiles were calculated (CGMS values subtract to PBGM value). The percentages of CGMS and PBGM nadirs below 90 mg/dL, above 160 mg/dL, and between 90 and 160 mg/dL were also determined.

For each investigator, the differences between the insulin doses deduced from the paired glucose profiles were calculated, which was followed by calculating the median and range of these differences. The Wilcoxon matched pairs test was used to analyze differences between treatment decisions that were based on the corresponding glucose profile. Finally, the proportions of insulin doses deduced from the CGMS profiles that were lower, higher, and equal to the insulin doses deduced from the PBGM profiles were calculated.

To analyze interobserver agreement on treatment recommendations, insulin doses were compared for CGMS and PBGM profiles separately among investigators using the Friedman test, followed by Dunn's multiple comparisons test. Significance was set at $P < .05$.

3 Results

A total of 21 paired CGMS and PBGM profiles from 13 diabetic cats were available for analysis. One pair of glucose profiles was generated in 8 cats, 2 pairs of profiles in 3 cats, 3 pairs of profiles in 1 cat, and 4 pairs of profiles in 1 other cat. In 1 cat, paired glucose profiles could not be obtained because the sensor of the CGMS failed to read the interstitial fluid glucose concentrations. In all other cases, calibration of the CGMS was straight-forward because glucose concentrations measured in the capillary blood with the PBGM were between 40 and 400 mg/dL. Representative paired glucose profiles from 2 diabetic cats are shown in Figure 1.

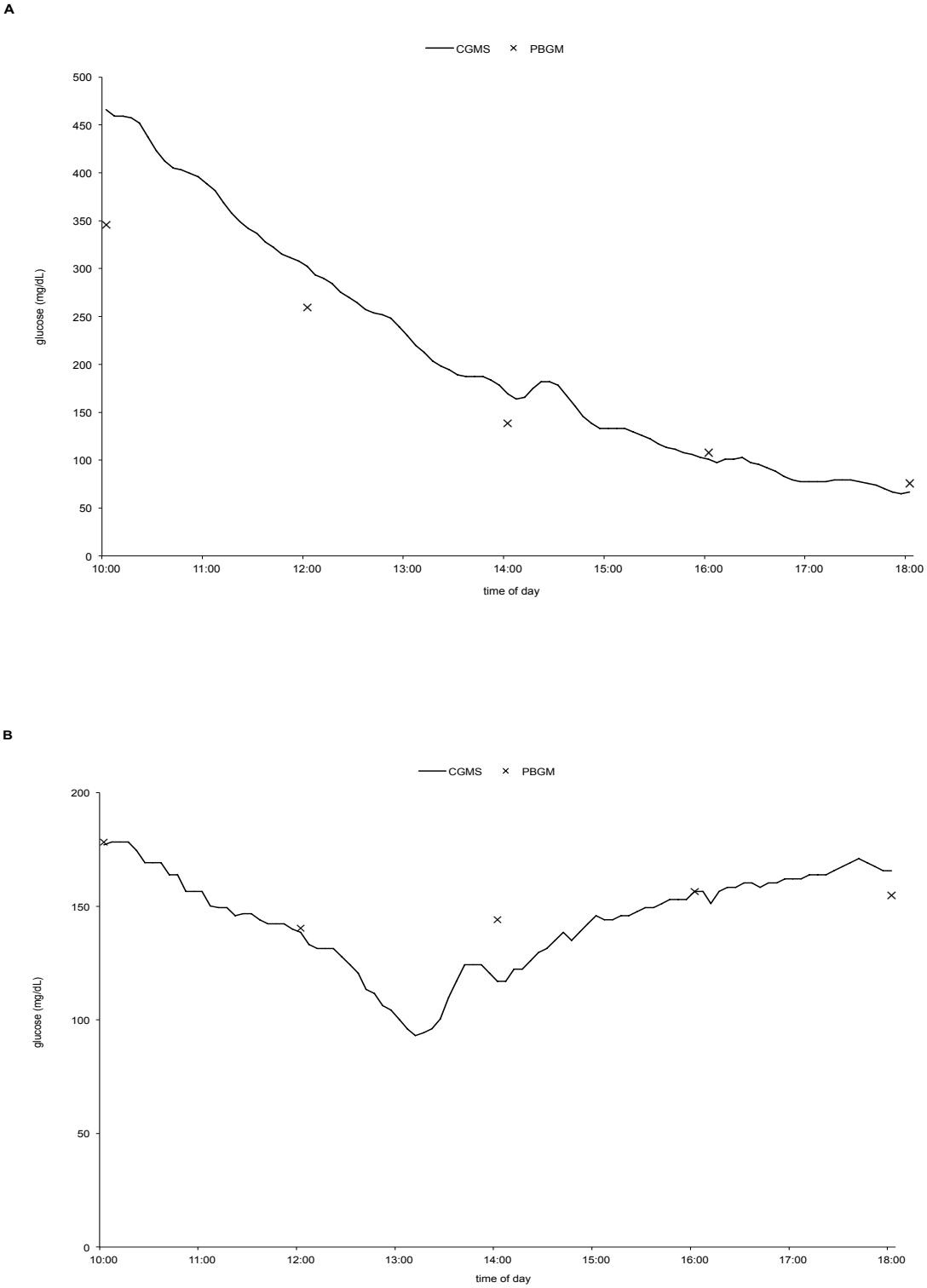
The median difference between glucose nadirs of the paired glucose profiles was -25.2 mg/dL (range -124.2 to +10.8). Compared with the PBGM profile, the nadir of the CGMS profile was lower, equal, or higher in 17 (81%), 2 (9.5%), and 2 (9.5%) profile pairs, respectively. Of the 19 pairs of glucose profiles in which the nadirs differed, the lowest glucose concentration was <90 mg/dL measured with the CGMS and between 90 and 160 mg/dL measured with the PBGM in 4 cases, and between 90 and 160 mg/dL measured with the CGMS and >160 mg/dL measured with the PBGM in 1 case. In the remaining 14 cases, paired nadirs were in the same range of glucose concentration (either <90 mg/dL, between 90 and 160 mg/dL, or >160 mg/dL). In 16 out of 21 cases, the CGMS nadir occurred within 2 hours from that of the PBGM; in 5 cases, the PBGM nadir anticipated that of the CGMS of 3.5–4.5 hours.

The median difference between glucose peaks of paired profiles was -45 mg/dL (range -307.8 to +91.8); the median difference between glucose means of paired profiles was -28.4 mg/dL (range -160.2 to +19.5).

There was no significant overall difference between the insulin doses deduced from the CGMS and PBGM profiles (p for examiner 1 = 0.22; p for examiner 2 = 0.13; p for examiner 3 = 0.12); the median difference between the doses was 0 U per injection and ranged from -1 to +0.5. Of the 21 pairs of corresponding glucose profiles, the three investigators deduced doses that differed from each other in 7 (33.3%), 4 (19.0%), and 8 (38.1%) pairs of glucose profiles, respectively. The dose deduced from the CGMS was lower than the dose deduced from the PBGM in five of the seven cases of investigator 1, in four of the four cases of investigator 2, and in six of the eight cases of investigator 3. There were no significant differences among investigators with respect to recommended insulin doses within profiles generated by the CGMS or within profiles generated by the PBGM.

Figure 1.

Paired CGMS and PGBM glucose profiles in diabetic cats. (A) This cat received 1.5 U insulin glargineb twice daily at home. Nadirs recorded with the 2 devices are similar. (B) This cat received 0.5 U insulin glargineb twice daily at home. The CGMS nadir is near to 90 mg/dL, whereas the PBGM nadir is approximately 140 mg/dL.



4 Discussion

Insulin dose adjustments after evaluation of glucose profiles generated by CGMS did not significantly differ from those obtained by the standard method PBGM. A study period of 8-10 hours was chosen to closely mimic the clinical setting, where a CGMS might be used during a 1-day hospitalization, similarly to glucose profiles generated with the PBGM. Because a CGMS measures glucose concentration more frequently, we hypothesized that 8–10 hour glucose profiles generated using the CGMS lead to insulin dose recommendations that differ from profiles generated using a PBGM. However, the overall treatment recommendations based on CGMS and PBGM profiles did not differ significantly, and the median recommended insulin doses differed by 0 U with a maximal divergence of -1 to +0.5. This suggests that treatment decisions based on CGMS profiles are generally similar to those obtained using PBGM profiles.

There was disagreement between the two insulin doses deduced from the two corresponding glucose profiles in 19 (30.2%) of the 63 treatment recommendations made by the three blinded investigators; in 15 of these, the dose deduced from the CGMS profile was lower than the dose deduced from the PBGM profile. A likely reason for this was that the CGMS provided glucose concentrations every 5 minutes and thus more detailed glucose profiles. This allowed the detection of nadirs that may not have been identified in glucose profiles generated by a PBGM, in which blood glucose concentration was determined every 2 hours. Because the nadir is crucial for determining the most appropriate insulin dose,[7] detection of lower nadirs with the CGMS may explain the differences in these dosage recommendations. Two of the corresponding nadirs were numerically identical and the remaining 19 differed; in 17 of the latter, the nadir of the CGMS profile was lower. Furthermore, in five of the 19 cases, the two corresponding nadirs were in different blood glucose ranges (high/ideal ranges in one case and ideal/low ranges in four), which highlights the potential for erroneous treatment decisions, particularly when relying on the PBGM (yielded higher nadirs). In one case, the difference between nadirs was particularly pronounced (ie, -124.2 mg/dL). The reason for this finding is unclear and may be due to dysfunction of the CGMS sensor or, possibly, to a very rapid change in blood glucose concentration leading to a delay in interstitial glucose fluid equilibration.[11] The latter may also have been responsible for the marked differences observed in one case for the glucose peak (ie, -307.8 mg/dL) and for the mean glucose concentration (ie, -160.2 mg/dL). In a previous study,[11] the time delay between a rapid rise in blood glucose and interstitial glucose concentrations measured with a CGMS was 11.4 minutes. It is assumed

that a rise in glucose concentrations after rapid blood glucose fluctuations would be read by the CGMS approximately 11 min after the PBGM.

In 16 cases paired nadirs occurred within 2 hours. However, in five cases the delay between PBGM and CGMS nadirs was of 3.5–4.5 hours; of note, in all five cases the PBGM nadir anticipated that of the CGMS. By examining CGMS profiles (data not shown) it was possible to observe that after insulin administration glucose concentrations dropped slowly and with some fluctuations in each case. Fluctuations might have been responsible for the apparently longer delay between nadirs.

Overall treatment recommendations did not differ among the three investigators with regard to CGMS or PBGM profiles, which suggested that the criteria used to assess the glucose profiles were reliable. In dogs, Davison et al,[14] evaluated the difference between treatment recommendation made by two examiners, using an earlier generation of CGMS together with a PBGM used as reference. Recommendations were equal in 12 out of 20 cases, leading the authors to conclude that the CGMS can be safely employed for clinical use in dogs with diabetes mellitus.

A major advantage of using the CGMS to generate glucose profiles during follow-up examinations is reduced restraint and handling of patients.[11] In particular, glucose concentrations are more reliably and easily monitored with a CGMS in frightened or aggressive cats. With regard to technical limitations encountered in this study, it is worth noting that in 1 cat, a CGMS profile could not be obtained because of sensor failure. Technical problems such as sensor failure or calibration errors may constitute drawbacks of using a CGMS for generating glucose profiles over an 8- to 10-hour period.[11] Of note, measurements obtained over 8–10 hours, although sufficient to generate glucose profiles in cats receiving insulin twice daily, may not be enough to evaluate treatment response and thus to give recommendations about insulin dose in cats previously treated with insulin once daily, especially if the insulin dose is administered in the evening.

Another drawback of the CGMS for generating short-term profiles is the relatively long initialization period (2 hours), during which glucose readings are not provided by the instrument. This is particularly relevant when diabetic cats can be hospitalized for only a few hours during follow-up examination. Furthermore, calibration is only feasible when glucose concentrations are between 40 and 400 mg/dL. Values outside this range are inadequate for calibration, which means that CGMS recordings are delayed until the blood glucose concentration has returned to within the working range of the instrument. Although this did not occur in the present study, glucose values above 400 mg/dL occur frequently in diabetic

cats with poor glycemic control. Finally, the few CGMS calibrations obtained for each glucose profile might have led to invalid assessment of insulin requirements in some cases. However, in the present investigation calibrations were performed as suggested by the manufacturer and as in previous CGMS studies in cats.[11,12]

In summary, insulin dose adjustments based on glucose profiles generated with the CGMS and PBGM are similar, suggesting that the former instrument is valuable for obtaining short-term glucose profiles in diabetic cats in a clinical setting. However, sensor failure and calibration delay may limit the usefulness of the CGMS. Better detection of nadirs with the CGMS may prove useful for improving adjustments in insulin dose in some diabetic cats. Further studies are needed to investigate whether long-term use of CGMS during follow-up examinations improves blood glucose control in diabetic cats.

5 References and Footnotes

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Footnotes

a Guardian REAL-Time continuous glucose monitoring system, Medtronic, Münchenbuchsee, Switzerland

b Lantus insulin, Sanofi Aventis, Geneva, Switzerland

c Sterilium, Bode AG, Münchenstein, Switzerland

d AlphaTRAK portable blood glucose meter, Abbot Animal Health, Maidenhead, UK

e GraphPad Prism 4.0, GraphPad, San Diego, CA

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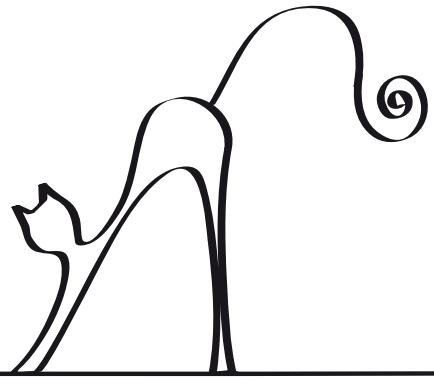

Lebenslauf

Name	Simona Gianna Dietiker-Moretti
Geburtsdatum	12.04.1983
Geburtsort	Locarno (TI)
Nationalität	Schweizerin
Heimatort	Castel San Pietro (TI)

1989 – 1994	Primarschule in Bellinzona
1994 – 1998	Sekundarschule in Bellinzona
1998 – 2002	Gymnasium in Bellinzona
2002	Kantonale Matura
2002 – 2007	Studium der Veterinärmedizin an der Vetsuisse Fakultät, Universität Zürich
2007	Staatsexamen an der Vetsuisse Fakultät, Universität Zürich
2008 – 2011	Doktorarbeit an der Klinik für Kleintiermedizin der Vetsuisse Fakultät der Universität Zürich
Seit 2009	Assistenzärztin bei der Abteilung Radio-Onkologie der Vetsuisse Fakultät der Universität Zürich

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